Effect of Postoperative Intravenous Acetaminophen versus Placebo, Combined with Propofol or Dexmedetomidine, on Postoperative In-Hospital Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial

# SUPPLEMENTARY APPENDIXES

**Contents**



This supplementary material has been provided by the authors to give readers additional information about their work.

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

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|---|---|
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| **Study Sponsor:** | Mallinckrodt Pharmaceuticals |
| **Study Coordinating Center:** | Beth Israel Deaconess Medical Center |
| **Original Protocol Version Date:** | 01/29/2015 |
| **IRB Protocol Number**: | 2014P000413 |
| **Clinicaltrials.gov NCT**: | NCT02546765 |

## STUDY PROTOCOL

**Purpose**

The goal of this randomized clinical trial is to evaluate the effect of intravenous (IV) acetaminophen vs placebo, combined with IV propofol vs dexmedetomidine, for postoperative sedation and analgesia respectively, in adult patients 60 years or older undergoing coronary artery bypass grafting (CABG) or combined CABG/valve surgeries to assess the incidence of postoperative delirium with the Confusion Assessment Method (CAM or CAM-ICU). It is possible that there may be a benefit to those enrolled in the dexmedetomidine and acetaminophen group, as their incidence of delirium could possibly be reduced, however we cannot guarantee this.

Additionally, this study will assess postoperative cognition following cardiac surgery through 1-year using a cognitive assessment scale and compare postoperative analgesic requirements in patients with and without IV acetaminophen.

**Study Summary**

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|---|---|
| **Title** | Effect of Postoperative Intravenous Acetaminophen versus Placebo, Combined with Propofol or Dexmedetomidine, on Postoperative In-Hospital Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial |
| **Objective** | To evaluate the effect of postoperative IV acetaminophen (paracetamol) vs placebo, combined with IV propofol vs dexmedetomidine, on postoperative delirium among older patients undergoing cardiac surgery |
| **Inclusion Criteria** | Patients 60 years or older undergoing CABG with or without aortic and/or mitral valve replacement requiring cardiopulmonary bypass |
| **Exclusion Criteria** | Patients with preoperative left ventricular ejection fraction (LVEF) <30%, pre-existing cognitive impairment, Alzheimer's disease, Parkinson's disease, medications for cognitive decline, history of recent seizures, serum creatinine >2 mg/dL, liver dysfunction, recent history of alcohol abuse, English language limitations, hypersensitivity to study medications, and undergoing emergent surgery |
| **Study Design** | Single center, randomized, triple blind, placebo controlled, factorial design clinical trial<br><br>Patients were randomized to one of four factorial groups which included randomization to receive postoperative analgesia with intravenous acetaminophen or placebo every 6 hours for 48 hours. In addition, patients were randomized to receive postoperative sedation starting at chest closure and continued for up to 6 hours postoperatively or until extubation with intravenous dexmedetomidine or propofol.<br><br>The incidence of postoperative in-hospital delirium was assessed daily using the CAM or CAM-ICU during the patient's hospitalization. In addition, follow up assessments were conducted at one month and one year. |
| **Study Discontinuation** | Patient request or any serious adverse event thought to be related to study procedures |
| **Key Roles** | *Principal Investigator*: Balachundhar Subramaniam, MD MPH<br><br>*Institution:* Beth Israel Deaconess Medical Center, Boston MA |

**Significance and Background**

Approximately 50% of patients have postoperative delirium following cardiac surgery[1]. The growing body of evidence suggests that in-hospital delirium is associated with poor hospital outcomes, including a tenfold increased risk of death, and a fivefold increased risk of nosocomial related complications[2]. Delirium has also been associated with serious longer term outcomes such as poor functional recovery, and most recently, impaired cognitive function for up to one year after cardiac surgery[3]. Importantly, intervenable factors, such as perioperative sedation and analgesia with opioids may contribute to the etiology of delirium. In the setting of cardiac surgery done increasingly in older patients, there is an urgent need to test alternative sedation and complementary analgesic techniques.

Dexmedetomidine, a selective alpha-2 receptor agonist, provides sedation without causing respiratory depression. Dexmedetomidine is also suggested to have an opioid sparing effect that makes it a unique sedative drug. Currently used sedation drugs (midazolam) release deliriogenic mediators through binding of Gamma-aminobutyric Acid (GABA) receptors. Dexmedetomidine has no effect on the GABA receptors. Although these characteristics suggest dexmedetomidine to be a unique and promising drug for sedation following cardiac surgery, its efficacy on reducing the incidence, duration and long term effects of delirium has not been studied thoroughly.

Studies involving use of dexmedetomidine in an attempt to reduce the incidence of delirium in cardiac surgical patients provide conflicting results. One meta-analysis concluded that dexmedetomidine in cardiac surgery shortened the ventilator time (but not the Intensive Care Unit (ICU) or hospital length of stay), reduced the incidence of postoperative ventricular arrhythmias and delirium in cardiac surgical patients[4]. However, there are several issues with this meta-analysis, particularly for the systematic assessment of postoperative delirium. The problems with the four studies that formed the basis of this meta-analysis are explained in the next few paragraphs.

In a retrospective study[5] of administrative database from 250 hospitals, the incidence of postoperative delirium following cardiac surgery was significantly decreased with associated cost savings in the dexmedetomidine group. This study compared two regimens (dexmedetomidine, propofol plus narcotics vs. propofol vs. narcotics). Propofol was used in the dexmedetomidine group as well. This trial specifically does not mention how delirium was assessed in individual hospitals.

A randomized controlled trial[6] comparing dexmedetomidine/propofol to morphine/propofol in cardiac surgery patients showed a decreased duration of delirium (5 days to 2 days) in the dexmedetomidine group. This study found a similar incidence of delirium in both the groups. Propofol was used as a sedative in both the groups and this could have attributed to similar incidences of delirium in both the groups. There is a possibility the study was not powered adequately as the baseline incidence of delirium in the control group was a surprisingly low 15%, much lower than other cardiac surgery studies that have employed state-of-the art delirium measures. This study used CAM-ICU for assessing delirium both in intubated and extubated patients. While the CAM-ICU, a delirium assessment that does not require any verbal responses by the patient, is state-of-the-art for intubated patients, it has reduced sensitivity for delirium in verbal patients. This design could have underestimated the incidence of delirium.

The third study[7] included in the meta-analysis was a prospective, randomized, open labeled trial comparing three groups (dexmedetomidine, midazolam, and propofol). This study reported a dramatically decreased incidence of delirium in the dexmedetomidine group, 3%, compared to 50% in propofol and midazolam groups. This was a small study, with only 118 patients were recruited and only 90 patients finally analyzed,

with 28 patients randomized patients excluded for protocol violations. This introduces a significant selection bias. Furthermore, a 94% reduction in the incidence of delirium was seen in this study. This effect size is almost implausibly large and has not been seen in other studies. Nevertheless, this study can provide a framework for sample size for future studies assuming the best case scenario.

The final study[8] included in the meta-analysis was a prospective randomized control trial of 89 patients undergoing non emergent CABG. In this study, a patient satisfaction questionnaire was used to assess pain, comfort and extubation process between intravenous dexmedetomidine and propofol groups. One patient in each group was reported to have delirium. This study was not designed to identify patients with delirium with any specific tools such as CAM and thus could have grossly underestimated delirium incidence. Thus, the meta-analysis represents a combination of poorly designed studies with differing measurements, and is extremely unlikely to create a significant impact or practice change among clinicians. Therefore, these findings will not result in a practice change in cardiac surgical intensive care units.

Postoperative pain following cardiac surgery can be due to the sternal incision, chest tube sites and leg incisions. Current pain relief strategy includes postoperative opioid administration (IV morphine or hydromorphone). While, inadequate pain relief increases the risk of postoperative delirium, opioids with their psychoactive properties also increase the risk of postoperative delirium, especially in elderly patients. A multimodal balanced postoperative pain management is advantageous and provides several beneficial effects. The options in cardiac surgery would include nonsteroidal anti-inflammatory drugs and acetaminophen. Their postoperative use decreases the exposure of older patients to opioids and can be an effective delirium prevention strategy. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) have contraindications after many kinds of surgery, including cardiac surgery, which include their deleterious effects on the gastrointestinal tract and renal function.

Acetaminophen has no psychoactive properties and is an attractive option as it lacks bleeding risks associated with nonsteroidal agents. Acetaminophen is for the most part safe but could cause liver dysfunction in rare instances. Oral administration of acetaminophen achieves limited blood levels in critically ill patients and therefore has limited efficacy. IV acetaminophen addresses this by allowing administration in critically ill patients and providing superior bioavailability to oral preparations[9]. This approach has been shown to reduce pain intensity and also decrease the rescue intravenous morphine used during the postoperative period.

IV acetaminophen has never been studied in the context of cardiac surgery and delirium prevention. Additionally, comparing IV acetaminophen as an adjuvant analgesic in combination with IV propofol or IV dexmedetomidine may ascertain additive or synergistic effects on delirium prevention. Our randomized, single-blind, pre-pilot study with 12 patients showed that in patients who received IV acetaminophen as adjuvant analgesic (N=6), the incidence of delirium was 17% (1/6) compared to 67% (4/6) in those who did not. The total incidence was 42% (5/12). Despite the small sample size, this provocative finding suggests that IV acetaminophen with propofol or dexmedetomidine may offer a significant benefit in reducing the incidence of delirium following cardiac surgery. If this benefit is proved in a larger study as proposed, this will have a significant impact in patient care and satisfaction.

**Subject Recruitment**

*Screening*

Eligible participants will be identified at preadmission testing clinic appointments, in the cardiac catheterization lab or on the medical floors. At this time all inclusion and exclusion criteria will be assessed.

*Inclusion Criteria*

Adult patients ≥ 60 years of age who are undergoing CABG with/without valve (aortic and/or mitral) procedure requiring bypass.

*Exclusion Criteria*

Patients will be excluded if they had a preoperative LVEF <30% emergent procedure, isolated aortic surgery, pre-existing cognitive impairment, Parkinson's disease, Alzheimer's disease, prophylactic medications for cognitive decline, active history of drug or alcohol abuse, serum creatinine >2mg/dL , liver dysfunction, non-English speaking, seizures in the last three months, emergent procedure or hypersensitivity to study drugs or procedures.

Adult patients unqualified or incapable of giving legal consent will be excluded.

**Informed Consent**

Written informed consent will be obtained prior to initiation of any study-specific procedures. Consent will be obtained by one of the participating researchers of the study. At the time of consent, all study procedures will be explained in detail, including the associated risks and benefits. The subjects will have the opportunity to ask any and all questions, and will be reminded that participation is voluntarily. All subjects will be consented with curtains drawn or the door closed, assuring patient privacy. Written informed consent will then be obtained from interested participants. The original signed form will remain with the investigator in the study file. Copies will be given to the patient and filed in the official medical record as well.

**Randomization and Blinding**

After obtaining written informed consent, participants will be randomized to one of four groups by the research pharmacy using a sequence of computer –generated random numbers. Blocked randomization will be used to assign recruited participants to one of four combinations of analgesics and sedatives in a 1:1:1:1 allocation: (1) acetaminophen and dexmedetomidine, (2) acetaminophen and propofol, (3) placebo and dexmedetomidine, or (4) placebo and propofol. In order to blind the patient, the care team, and the research staff assessing outcomes to the analgesia group, 1 gram of IV acetaminophen and placebo (0.9% saline) were distributed in equal volume IV bags. Due to the distinct appearance of propofol, there was no blinding to the sedation group.

**Study Procedures**

*Overview*

The proposed study is a randomized, placebo controlled, factorial design, triple blind, clinical trial designed to evaluate the effect of postoperative IV acetaminophen versus placebo, combined with IV propofol versus dexmedetomidine, on postoperative delirium among older patients undergoing cardiac surgery. Patients will be randomized to one of four groups (1) acetaminophen and dexmedetomidine, (2) acetaminophen and propofol, (3) placebo and dexmedetomidine, or (4) placebo and propofol. It is possible that the participants who receive acetaminophen and dexmedetomidine may benefit from the study as their incidence of delirium could possibly be reduced, however we cannot guarantee this.

*Study Groups*

The four treatment arms will be:

1. Acetaminophen and dexmedetomidine
2. Acetaminophen and propofol
3. Placebo and dexmedetomidine
4. Placebo and propofol

All study medications will be administered intravenously and doses will be weight-based. Acetaminophen/placebo will be administered on ICU transfer and thereafter every six hours for a total of eight doses. Volume of the placebo (saline) will match that of IV acetaminophen at 100ml 0.9% sodium chloride. Acetaminophen administration in any form other than the blinded study medication during this time was not allowed. Propofol or dexmedetomidine was started during chest closure and continued for up to six hours postoperatively or until extubation, whichever occurred first. Participants in the dexmedetomidine groups will get a bolus dose of 0.5 - 1mcg/kg IV during chest closure, followed by a maintenance infusion of 0.1 -1.4 mcg/kg/hour. Propofol infusions will be avoided in these participants. Patients in the propofol groups will receive propofol at a dose of 20 – 100 mcg/kg/min and dexmedetomidine infusions will be avoided in these patients.

*Pharmacy*

Once a participant is enrolled, the study team will contact the research pharmacy to randomize the subject. The research pharmacy at Beth Israel Deaconess Medical Center will be responsible for preparation and distribution of study medications. Study team members will physically deliver the first dose of the acetaminophen/placebo (saline) medication. Subsequently the research pharmacy will be responsible for delivering the study medication to the ICU. Any unused drug will be returned to the research pharmacy for disposal.

*Study Assessments*

The assessments will be completed at specific time points. Once consent is obtained, a trained study team member blinded to treatment allocation will proceed with a baseline cognitive and delirium assessment. This will include the assessment of cognitive function using the Montreal Cognitive Assessment (MoCA), supplemented with days of the week backwards (DOWB) and months of the year backwards (MOYB) for additional attention testing, the Delirium Symptom Interview (DSI) to capture symptoms of delirium and the Geriatric Depression Scale (GDS) to assess for baseline depression. Using data from the cognitive testing and DSI, a study team member will complete the Confusion Assessment Method (CAM), which includes a diagnosis of delirium using the CAM diagnostic algorithm. This detailed assessment will take no more than 20-30 minutes. Every day, a study team member will administer a standard cognitive assessment and the CAM. These daily assessments will take approximately 10-15 minutes. On the day of discharge, the MoCA with DOW and MOY, the DSI, and CAM will be completed. (If the discharge assessment was performed in anticipation of discharge on a specific day but the discharge was delayed (i.e. logistical reasons, clinical reasons), this will not be considered a protocol deviation.) A follow-up assessment will be administered at 1 month and 1 year post-discharge over the telephone and will include a telephone version of the MoCA known as the T-MoCA, DSI, GDS, and CAM. Assessments will be administered and scored by trained study team members.

If daily assessments are negative for three consecutive days (i.e. days 5, 6 & 7), they will then be completed every other day until date of discharge. In addition, these assessments will be done at the patient's convenience to ensure ability to finish the evaluations. The table below outlines the assessments at various time points.

| Assessments | Baseline | Daily | Discharge | 1 month | 1 year |
|---|---|---|---|---|---|
| Montreal Cognitive Assessment (MoCA) with Days of the week (DOW) & Months of the year (MOY) | X | | X | | |
| Delirium Symptom Interview (DSI) | X | X | X | X | X |
| Geriatric Depression Scale (GDS) | X | | | X | X |
| Confusion Assessment Method (CAM) | X | X | X | X | X |
| Standard Cognitive Assessment | | X | | | |
| Telephone Montreal Cognitive Assessment (t-MoCA) with DOW and MOY | | | | X | X |

The delirium research assessments will not be provided to the treating clinicians. Treating clinicians will assess and treat delirium as usual, including assessment and correction of reversible causes, behavioral management and use of IV haloperidol for agitation, if needed. Rescue doses of haloperidol will be recorded in the study.

*Blood Acquisition*

Blood will be collected at four times points 1) Baseline: at the time of the pre-operative study assessments or on day of surgery; 2) on POD 1 while in the intensive care unit; 3) on POD 2 while in the intensive care unit; and 4) within 48 hours prior to discharge or days 8-10, at the latest. A total of 80 ccs of blood will be collected. Blood samples will be collected into sterile vacuum tubes using either a vacutainer or butterfly system, at the preference of the phlebotomist. All samples will be centrifuged. The plasma and buffy coat will be separated from red blood cells, aliquoted into small samples, labelled and frozen at -80 Celsius for future use. Blood samples will be stored in a biomarker bank for further analysis.

*Blood Storage*

Using all blood samples from our participants, we will create a bio-repository of genetic material and plasma, a resource for future biomarker discovery studies. The banked specimens will be coded and stored in a -80 Celsius freezer at a BIDMC facility. A list linking study numbers to participants will be kept in a secure computer database. In the future, the frozen plasma or DNA may be shared with other scientists studying a similar relationship between delirium and genetic factors after a formal application procedure and scientific review process approved by the IRB. Information including contact information, rationale for studying data and intended use of data may need to be approved by CCI/IRB prior to sharing data. All such studies will be carried out under controlled access and under the close supervision of the study team. In these cases, the study investigators will maintain confidentiality of the specimens by maintaining the de-identification of

patient information to the other scientists. We plan to store these specimens indefinitely. None of the results from these studies will be shared with participants or their family members and none of the genetic information obtained will be included in the patient's medical records. All patients approached for participation in study will also need to agree to participation in blood collection/storage as noted in informed consent.

*Follow Up*

A follow-up assessment will be administered at 1 month and 1 year post-discharge over the telephone and will include a telephone version of the MoCA known as the T-MoCA, DSI, GDS, and CAM.

**Study Outcomes**

*Primary Outcome*

The primary objective of this study was the incidence of in-hospital delirium at any time during a patients' hospital stay.

*Secondary Outcomes*

The secondary outcomes included duration of delirium, postoperative neurocognition at discharge, 48-hour breakthrough analgesic requirements, and ICU and hospital lengths of stay.

*Data Collection*

The participant's demographic data such as age, sex, ethnicity, race and body mass index will be recorded. Patient comorbid conditions, surgery and anesthetic drugs used will be obtained from Society of Thoracic Surgery database and Anesthesia Information Management System, which is a clinical outcomes registry that records and assesses the care of adult patients undergoing cardiac procedures at participating hospitals. Pertinent characteristics include: preoperative medications, comorbidities, surgical characteristics, and postoperative outcomes, including 30 day mortality and major adverse events like renal failure during hospital admission. Information on the sedatives and analgesics given within six hours prior to initiation of the cognitive assessment will be recorded, as to determine whether there is an effect on performance. The total opioid dosage administered during the first 48 hours post operatively, pain scores and patient delirium assessment data will be collected using REDCap. REDCap is a web-based application that allows customized data collection and entry. The study team will build and maintain the case report form electronically. Additionally, internal audits will be conducted to ensure data completion and data quality. Data will be kept secure in computers with password protection. All data will be analyzed with modified intention to treat basis, in which all subjects who receive at least one dose of a study medication will be included.

**Data Security and Storage**

All data will be kept secure in the password-protected BIDMC network servers. The paper format will be stored in locked file cabinets during the study period. Study data will be entered in datasheets and stored on a secure password-protected computer on the BIDMC network. Each patient will be assigned a study-specific ID number. The data will have all HIPAA identifiers removed and a random study number assigned to each patient.

**Safety Reporting**

Our patient population is by definition undergoing high risk surgery and is critically ill. It is expected that they will have a number of unrelated adverse health events during the course of their hospital stay. The potential adverse effects such as the number of episodes of hypotension (predefined as < 90mm systolic for 5 minutes or more), and bradycardia (predefined as <40 beats per minute), will be collected from the ICU charts.

Therefore, we will limit the scope of our AE monitoring and reporting to the following:

- All Serious Adverse Events, including an unexpected death, believed to be related to the study
- Unexpected, non-serious Adverse Events believed to be possibly or probably related to the intervention

Evidence for adverse events will be assessed daily during the hospital stay, for a maximum of 10 days.

**Statistical Analysis**

Please refer to the Statistical Analysis Plan (SAP) for details of the power calculation and analyses.

**Benefits to the Subject**

There is a possible benefit to those enrolled in the dexmedetomidine and acetaminophen group, as their incidence of delirium can possibly be reduced, however we cannot guarantee this. Society as a whole will benefit in the future as a result of knowledge gained from the research.

**Risks to the Subject**

*Risk of the Drugs Used*

The drugs dexmedetomidine and acetaminophen are FDA approved for sedation and analgesic purposes. Bradycardia and hypotension are less common side effects with dexmedetomidine and in an intensively monitored setting of cardiac surgical ICU, the risks of bradycardia and hypotension can be managed effectively. Liver dysfunction is a rare side effect associated with IV acetaminophen. However, the drug is commonly used already in the perioperative setting routinely as the benefits seem to outweigh the risks. No routine monitoring is done for liver dysfunction in the current standard of care.

*Risk Associated with Blood Draw*

There is a small risk of phlebotomy to obtain serum for the serum biomarker assays at four time points during the study. Wherever possible, the serum collection will be obtained at the same time as phlebotomy and other labs for routine clinical laboratory work, thereby eliminating an additional risk imposed by a separate phlebotomy for study purposes. However, in rare cases such as at the time of discharge, patients may require a separate lab draw. The risks of the phlebotomy procedure itself are minimal and are primarily related to pain or bruising at the needle puncture site. Since the amount of blood required at each time point is small the risks from anemia or blood loss are negligible. The blood draws will total only 80 cc's over a maximum of four weeks, which is considered minimal risk.

*Risk of Breach of Confidentiality*

Patients will be referred to by a study number, and records will be password protected on BIDMC network servers. No identifiable data will be shared with the funding agency, or across institutions. The information that we collect from this research project will be kept confidential. All information will be stored in a HIPAA compliant database.

*Risk/Benefit Ratio*

The drugs used for this study are approved by the FDA for sedation and analgesic purposes. When monitored in the intensive care setting, the risks of lower blood pressures or heart rates are far too small compared to the benefits of decreased delirium following cardiac surgery.

**Inducements**

No inducements will be offered. Neither patients nor healthcare providers will be paid as part of their participation in the study.

**Participant Withdrawals**

Throughout the study participants will be reminded that participation is entirely voluntary and that they have the option to withdraw at any time, for any reason.

**Subject Protection**

Patients will be contacted directly for this study. The informed consent will be explained and obtained in a secure and private location such as the preadmission testing clinic, cardiac catheterization holding areas, cardiac surgery clinic, and/or in the pre-operative holding area. Patients will be informed that their decision to participate or not to participate will in no way affect their relationship with their health care provider. Furthermore they will still receive all information about their analgesic management, as is the standard of care. Patients will also have the ability to discontinue their participation at any time.

# STATISTICAL ANALYSIS PLAN

## Introduction

This Statistical Analysis Plan describes the analysis of the prospective randomized controlled trial that has been reviewed and approved by the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center (2014P000413) and will be conducted in accordance with all applicable human subjects' research requirements and applicable federal regulations.

## Study Aims

Briefly, this randomized, factorial clinical trial evaluates the effect of intravenous acetaminophen versus placebo, combined with intravenous propofol versus dexmedetomidine, for postoperative sedation and analgesia respectively, in adult patients 60 years or older undergoing coronary artery bypass grafting (CABG) or combined CABG/valve surgeries to assess the incidence and duration of postoperative delirium.

## Study Design

This is a single-center randomized controlled factorial trial of two sedative and two analgesic regimens.

## Study Population and Sites

The study will prospectively enroll patients undergoing cardiac surgery at Beth Israel Deaconess Medical Center in Boston, Massachusetts. This includes patients enrolled between September 2015 and April 2018.

## Randomization

Randomization will be by pre-prepared using a computer generated block randomization in SAS 9.3. Details of the block size are kept confidential until the completion of study enrollment. This schema will be created by the unblinded statistician (Ariel Mueller, MA) and sent to the research pharmacy. Members of the research pharmacy will be responsible for preparing and dispensing the study medications following an active order for study medications. Specifically this includes preparation and blinding of the placebo in accordance with the study randomization schema.

Patients will be randomized to one of four groups in a 1:1:1:1 fashion. This includes:

- Acetaminophen and Dexmedetomidine
- Acetaminophen and Propofol
- Placebo and Dexmedetomidine
- Placebo and Propofol

## Primary Endpoints

The primary endpoint will be the incidence of in-hospital delirium. This is assessed via the Confusion Assessment Method (or CAM-ICU for intubated patients) daily postoperatively, as specified in the study protocol. If a patient is noted to be positive for delirium on any postoperative day, they will have been documented as achieving the primary study endpoint.

Our pre-specified primary analysis will assess the incidence of delirium between patients receiving IV acetaminophen versus placebo.

## Secondary Endpoints

Secondary outcomes for this study include:

- Duration of delirium

  - *Definition: The number of days of being positive for delirium on the CAM or CAM-ICU instruments will be recorded and assessed. This will be assessed as a continuous variable.*
- Postoperative cognitive decline at discharge, one month and one year postoperatively
  - *Definition: This will be assessed by using the change in Montreal Cognitive Assessment score at this time point since baseline. This will be assessed as a continuous variable.*
- Breakthrough analgesic requirements within the first 48 hours postoperatively
  - *Definition: This will be assessed by calculating the total morphine equivalent administered in the first 48 hours postoperatively, with time zero starting at ICU admission. This will be assessed as a continuous variable.*
- Intensive care unit (ICU) length of stay
  - *Definition: This will be defined as the number of hours admitted in the ICU prior to transfer to the general floor. This will be assessed as a continuous variable and reported in hours.*
- Hospital length of stay
  - *Definition: This will be calculated as the day of hospital discharge minus the day of surgery plus one. This will be assessed as a continuous variable and reported in days.*
- Predefined potential adverse effects of the study drugs including:
  - Number and duration of episodes of hypotension
    - *Definition: This is predefined as less than 90 mm Hg systolic blood pressure for five minutes or more*
  - Number and duration of episodes of bradycardia
    - *Definition: This is predefined as less than 40 beats per minute.*
- The proportion of patients who complete the protocol successfully will be measured.
- If this sedation and analgesic regimen is abandoned by the clinicians, the reason will be qualitatively described at the end of the study.
- Levels of inflammatory biomarkers

**Covariates**

Trial data will be collected managed using REDCap electronic data capture tools hosted at Beth Israel Deaconess Medical Center. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The REDCap system includes validation rules for data entry to help ensure data accuracy, and has a full audit trail of data entry and changes.

Data collection includes the participant's demographic data such as age, sex, ethnicity, race and body mass index will be recorded. Patient comorbid conditions, surgery and anesthetic drugs used will be obtained from Society of Thoracic Surgery database and Anesthesia Information Management System, which is a clinical outcomes registry that records and assesses the care of adult patients undergoing cardiac procedures at participating hospitals. Pertinent characteristics include preoperative medications, comorbidities, surgical characteristics, and postoperative outcomes, including 30 day mortality and major adverse events like renal failure during hospital admission. Information on the sedatives and analgesics given within six hours prior to initiation of the cognitive assessment will be recorded, as to determine whether there is an effect on performance. The total opioid dosage administered during the first 48 hours post operatively, pain scores and patient delirium assessment data will be collected using REDCap.

The overall flow and reporting of study recruitment, enrollment and follow up will follow the CONSORT recommendations for the reporting of randomized controlled trials.

**Sample Size Estimation**

This is a prospective, randomized, placebo controlled, double-blinded, factorial design study consisting of 120 patients to assess the incidence and duration of postoperative delirium following cardiac surgery. From the previous delirium studies conducted at our institution, the baseline delirium incidence was 50%. The pilot study showed a 66% reduction in the incidence of delirium. For the power calculation, a 50% reduction in the delirium incidence was used. Each group needed 56 patients (alpha=0.05 and 1-Beta=0.80). This study will not be powered for secondary outcomes.

Because complete data from 112 patients is required in order for analysis, we plan to enroll enough patients to obtain data from 120 patients who received the study intervention (60 patients per group - acetaminophen vs. no acetaminophen). We estimate that approximately 150 patients will be enrolled (consented) in order to achieve this sample size. This increase is required because it is possible that patients can be withdrawn both before randomization (i.e. cancelled surgery) as well as after randomization but before receiving the study intervention (i.e. change in surgery type intraoperatively). Enrollment will be stopped once a total of 120 randomized patients have undergone surgery and received the study medications.

**General Approach to Statistical Analyses**

Baseline and demographic characteristics will be summarized and presented using descriptive statistics. Continuous data will be presented as means ± standard deviations or medians (interquartile range) depending on the distribution of the data. The Shapiro-Wilk test will be utilized in order to determine whether or not the data follows a Gaussian distribution. Differences in continuous data between study groups will be assessed using a parametric t-tests or Wilcoxon Rank-Sum tests as appropriate. Categorical data will be presented as frequencies and proportions and assessed with a chi-square test. In the event that cell counts are small (less than 5), we will employ the use of a Fisher's Exact test. For all analyses two-sided p-values less than 0.05 will be considered statistically significant. SAS 9.3 (SAS Institute Inc., Cary, NC) or later will be utilized for all analyses.

Analyses will be performed on a modified intention to treat basis, in which all patient who receive at least one dose of any of the four study medications will be included.

**Analysis of the Primary and Secondary Outcomes**

The DEXACET trial has been designed as a factorial, randomized controlled trial with four treatment groups. We will therefore aim to test 1) the effect of acetaminophen versus placebo and 2) the effect of dexmedetomidine in comparison to propofol in the event that there is no interaction between treatment effects. However, the first of these (the effect of acetaminophen) is considered the most interesting and the study has been powered to answer this question using an unadjusted chi-squared test.

To test whether or not there is an interaction we will compose a logistic regression model include indicator variables for the acetaminophen group as well as the dexmedetomidine group. We will further include an interaction term in this model composed of the indicator variables multiplied together. If there is a significant interaction between groups when assessing the incidence of in-hospital delirium, we will interpret the results stratified by all four groups, presenting the main effects only after taking into account the other factor, in a 'inside the table analysis'. If the interaction term is not significant we will present the main effects by pooling data across the other factor.

Kaplan Meier curves and a Cox proportional hazards model was used to compare time to experiencing delirium, after confirming the proportional hazards assumption is met. To test whether the Proportional

Hazards (PH) assumption holds, we will include a time varying covariate with group in the model. Given the factorial design this approach will be replicated in models for all four factorial groups, as well as the pairwise comparisons (dexmedetomidine vs propofol; acetaminophen vs placebo) to ensure this assumption remains valid. In the event that this assumption is not valid, we will include a time-varying covariate in the model. Hazards ratios and their associated 95% confidence intervals will be reported.

Repeated measures analyses including generalized estimating equations with robust variance will be employed to assess for differences in continuous variables that are measured at multiple time points over time between groups using mixed model regression.

Interrater reliability assessments of delirium will be assessed for approximately 10% of patients. This includes assessment of both for the presence of delirium, and for key features including acute change, inattention, disorganized thinking and an altered level of consciousness. Percent agreement, kappa and weighted kappa will be reported.

Given the nature of a randomized controlled trial, we do not anticipate seeing differences between groups in baseline characteristics; however, we will perform a secondary analysis, adjusting for any differences observed between groups and presenting adjusted odds ratios and their associated 95% confidence intervals.

**Interim Analyses**

There will be no interim analysis.

**Missing Data**

The frequency and percentage of missing values for each variable will be collected, analyzed and reported as necessary. If there are missing values for the outcome variable(s), individual patients will be excluded. Highly incomplete covariates (>33% of observations missing) will be excluded from analyses. In the event that a variable is missing more than 10% of the time we will consider imputation. If missing values are missing at random (MAR) or not at random (MNAR), multiple imputation will be performed. Missing values, selection or exclusion of observations and variables and handling of missing values in the statistical analysis will be describes carefully and sensitivity analysis will be provided in the manuscript.

**Statistical Analytical Issues**

*Adjustments for Covariates*

Given the randomized nature of this study, there will be no covariate adjustment in the primary analysis. If differences between groups persist after randomization we will perform a post hoc analysis including variables that are significantly differ between groups.

*Multiple Comparisons*

There will be no adjustment for multiple testing. Results of secondary outcomes and post hoc analyses will therefore be considered exploratory.

**Examination of Subgroups**

Our pre-specified primary analysis will assess the incidence of delirium between patients receiving intravenous acetaminophen versus placebo. Predefined subgroup analyses will be performed for our primary and secondary outcomes for the following groups:

- Two sedative groups: dexmedetomidine versus propofol

- All four factorial groups including both sedatives (dexmedetomidine and propofol) and analgesics (acetaminophen and placebo).

**Post-hoc Analyses**

Post-hoc data driven analyses are allowed after the following are undertaken:

(a) Document which analyses were conducted after the results for the Primary and Secondary Aims are analyzed.
(b) Document the rationale for these analyses.
(c) Pre-specify their interpretation in the context of the primary and secondary results and their impact on the overall trial conclusions.

**eAPPENDIX 2. FAST TRACK PROTOCOL AND INTRAVENOUS DRUG ADMINISTRATION GUIDELINES**

## FAST TRACK PROTOCOL FOR CARDIAC SURGERY

| | |
|---|---|
| **Version:** | 12/2015 |
| **Institutional Authors:** | BIDMC Perioperative Cardiovascular Intensive Care Unit Committee |

### Cardiac Surgery Fast Track Ventilator Weaning Guideline

**Purpose**: Patients who have undergone an uncomplicated cardiac surgical procedure should be able to wean quickly from the ventilator, fostering a more rapid recovery. The fast track weaning guideline provides a decision-making framework that will expedite the process of weaning most efficiently

**Patient Selection**: Selection of patients for fast track ventilator weaning will be made at time of handoff in Cardiovascular Intensive Care Unit (CVICU). It is a collaborative decision by the healthcare team at which time an order is placed in the system.

Ventilator Settings on Arrival

All patients are placed on: assist control positive end expiratory pressure (PEEP) 5, fraction of inspired oxygen (FiO2) 100%, tidal volume (vT) 6-10 ml/kg (ideal body weight) and respiratory rate 12-14 (or per anesthesia)

Extubation Goal (4 hours for Fast Track)

- Nurse will write time of arrival on White Board
    - This allows all members of the team to know when 23 hours is up to prevent Society of Thoracic Surgeons (STS) designation of prolonged ventilation

### PRE-EXTUBATION

**I. Hand Off**

- Patient designated as appropriate for fast track wean
    - CVICU Nurse
    - Anesthesia
    - Intensive Care Unit (ICU) Provider
    - CVICU Respiratory Therapist (RT)

**II. Difficult Airway**

- ICU Provider, Intensivist, Registered Nurse (RN), and RT discuss plan in detail
    - Who needs to be notified when patient ready to extubated?
    - Does ICU Provider or Intensivist want to be present for extubation?
    - What additional equipment is needed at the bedside?

**III. Rewarming Guidelines**

- All Patients on arrival
    - Change intravenous fluid (IVF) to warmed IVF
    - Warmed blankets
    - Hourly temperature for the first 4 hours postoperatively
    - Record temperature prior to administration of reversal agents
- If Temperature ≤ 36°C (96.8°F)
    - Bair Hugger set at 42°C
    - May remove when temp > 36°C (96.8°F) for at least one hour
    - Suggest defer bath until > 36°C for at least one hour
- Nasal Thermometer Probes
    - May be used if still in place from Operating Room (OR)
    - Should be removed when reversal agents are administered or at 8 hours, whichever comes first
    - If accuracy is being questioned, switch to oral temperatures

**IV. Weaning Criteria**

| **Patient Criteria for Ventilator Weaning** | |
|---|---|
| **Parameter** | **Criteria** |
| Richmond Agitation-Sedation Scale (RASS) | +1 thru -1 |
| Cardiac Index | ≥ 2.0 L/min/$m^2$ |
| Mean Arterial Pressure (MAP) | > 60mm Hg < 80mm Hg |
| Cardiac Rhythm | Stable |
| Inotropic Support | No more than one inotropic drip |
| Chest Tube Drainage | < 100 ml/hour |
| Core Temperature | ≥ 35 $^{o}$C |
| pH | ≥ 7.32 |

**V.** Page ICU Provider at time patient placed on Continuous Positive Airway Pressure (CPAP) 5/5

- Notify provider if cuff leak present or not

**VI.** Arterial Blood Gas (ABG) should be obtained 30 minutes after placed on CPAP

- Patient condition may warrant earlier sampling to expedite extubation
    - Should discuss with team

**EXTUBATION**

**VII. Extubation Criteria**

| **Patient Criteria for Extubation** | |
|---|---|
| **Parameter** | **Criteria** |
| Strength | Able to lift and hold head for ≥ 5 sec |
| RASS | +1 to -1 |
| Heart Rate | 60-100 |
| Cardiac Index | ≥ 2.0 L/min/$m^2$ |
| MAP | > 60mm Hg < 90mm Hg |
| Cardiac Rhythm | Stable |
| Inotropic Support | No increase |
| Chest Tube Drainage | < 100 ml/hour and not increasing |
| Core Temperature | ≥ 36$^o$ C (96.8°F) |
| Respiratory Rate | 10-24 bpm |
| ABG on following settings:<br>CPAP FiO2 ≤ 50% PEEP 5 PS 5 | pH 7.34-7.45; pCO2 35-45; PaO2 ≥ 80 |

**VIII.** If not within fast track criteria then page the ICU provider immediately to discuss plan of action and if not ready for extubation return to step IV.

**IX. Meets Extubation Criteria**

- Decision to proceed with extubation may be made by the CVICU RN, in coordination with the CVICU RT
- For patients with a difficult airway, the plan to extubate should be discussed with the intensivist and ICU provider, prior to extubation

**X. Extubate**

- Head of Bed (HOB) should be elevated at least 60° unless contraindicated
- Endotracheal Tube (ETT) should be suctioned prior to extubation, with hyperoxygenation of the patient before and after suctioning (use the Suction 100% function on ventilator).
- Suction mouth with Yankauer immediately prior to extubation.
- Nasogastric tube, if present, should be aspirated and discontinued.
- Explain procedure to patient, informing them that a strong cough will be necessary as the ETT is withdrawn; explain that patient may be unable to speak for a time.
- Patient to be placed on face tent/nasal cannula to provide adequate $SpO_2$ ≥ 92%

**POST-EXTUBATION CARE**

Over the next several hours, oxygen should be weaned to maintain peripheral capillary oxygen saturation ($SpO_2$) ≥ 92%.

| **Nasal Cannula $O_2$ Flow / $FiO_2$** | |
|---|---|
| **Oxygen Flow L/min** | **Approximate $FiO_2$** |
| Room Air | 21% |
| 1 L/min | 24% |
| 2 L/min | 28% |
| 3 L/min | 32% |
| 4 L/min | 36% |
| 5 L/min | 40% |
| 6 L/min | 44% |

- ABG 30 minutes after extubation only if clinical suspicion of poor respiratory function
- Continuous SpO2 Monitoring
- Observation and assessment of patient for respiratory distress or increased work of breathing
- Incentive Spirometry (IS) every 30 min x 4, every 1 hour x 4; then hourly while awake or more often, as indicated
- Dangling on edge of bed within 2 hours should be performed unless contraindicated
- Patient/Family instruction in use of splint pillow during coughing and deep breathing
- Patient instruction in pain control as an important part of improved ventilation
- Position with HOB > 45, or up in chair, for enhanced respiratory pattern/coughing
- Weaning of FiO2 as tolerated to $SpO_2$ >92%

## INSTITUTIONAL INTRAVENOUS DRUG ADMINISTRATION GUIDELINES

| | |
|---|---|
| **Version Date:** | 01/2002 |
| **Revision Date:** | 11/2014 |
| **Medication:** | Dexmedetomidine Hydrochloride (PRECEDEX) |

Beth Israel Deaconess Medical Center

***IV DRUG ADMINISTRATION GUIDELINE***

**(Dexmedetomidine Hydrochloride (PRECEDEX®)**

**pH 4.5-7**

**Therapeutic category:** Alpha 2-Adrenergic Agonist Sedative

**Therapeutic Use**: Short term sedation of mechanically ventilated patients, or selected non-intubated patients in the intensive care setting, adjunct treatment for alcohol withdrawal in the intensive care setting.

**IV PUSH**

Not recommended

**INTERMITTENT INFUSION**

Not recommended

**CONTINUOUS INFUSION**

Maintenance infusion is 0.4 – 1.4 mcg/kg/hr.

**CLINICAL CONSIDERATIONS**

- **IV access:** May be administered peripherally or centrally
- **IV infusion device:** Sigma infusion pump required
- **Infusion related considerations:**
  - Continuous infusion should be titrated in 0.1- 0.2 mcg/kg/hr increments no more than every 30 minutes.
  - Acute agitation while titrating infusion should be managed with either midazolam or fentanyl bolus dosing – **Do not bolus dose dexmedetomidine** for ICU sedation
  - When converting a patient from other continuous sedation, dexmedetomidine should be initiated at 0.4 mcg/kg/hr for 1-2 hours before attempting weaning of other sedative agents.
  - Patients may remain on dexmedetomidine after extubation, (or to avoid intubation in alcohol withdrawal) but care should be taken to monitor hemodynamics and respiratory status (as below)
- **Monitoring:**
  - Patient should be continuously monitored for heart rate and blood pressure
  - Dexmedetomidine may prolong PR interval.
  - While dexmedetomidine does not cause respiratory depression, cases of obstructive apnea have been reported with high doses. Monitor continuous oxygen saturation while infusing
  - Level of sedation. (RASS) should be monitored at least every 4 hours
  - Common adverse effects include bradycardia and hypotension.

**COMPATIBILITY**

- Compatible with 0.9% Sodium Chloride
- Dexmedetomidine standard concentration: 400mcg/100mL
- Stable for 48 hours at room temperature. Do not refrigerate

**WRITTEN BY:** John Marshall, PharmD
**APPROVED:** Pharmacy and Therapeutics Committee
**DATE:** January 2002
**REVISED:** November 2014
**STATUS:** Formulary

**References**:

Shehabi Y et al. Clinical Application, The Use of Dexmedetomidine in Intensive Care Sedation. Crit Care & Shock 2010 Vol.13:(2); 40-50

**REFERENCES**

1. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation.* 2009;119(2):229-236.
2. Inouye SK. Delirium in older persons. *N Engl J Med.* 2006;354(11):1157-1165.
3. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med.* 2012;367(1):30-39.
4. Lin YY, He B, Chen J, Wang ZN. Can dexmedetomidine be a safe and efficacious sedative agent in post-cardiac surgery patients? a meta-analysis. *Crit Care.* 2012;16(5):R169.
5. Dasta JF, Jacobi J, Sesti AM, McLaughlin TP. Addition of dexmedetomidine to standard sedation regimens after cardiac surgery: an outcomes analysis. *Pharmacotherapy.* 2006;26(6):798-805.
6. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiology.* 2009;111(5):1075-1084.
7. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics.* 2009;50(3):206-217.
8. Corbett SM, Rebuck JA, Greene CM, et al. Dexmedetomidine does not improve patient satisfaction when compared with propofol during mechanical ventilation. *Crit Care Med.* 2005;33(5):940-945.
9. Holmer Pettersson P, Jakobsson J, Owall A. Plasma concentrations following repeated rectal or intravenous administration of paracetamol after heart surgery. *Acta Anaesthesiol Scand.* 2006;50(6):673-677.